UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,262	02/05/2005	William Malcolm Charles Rosenberg	3769.1000-000	3832

21005 7590 06/11/2008

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
06/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,262	ROSENBERG, WILLIAM MALCOLM CHARLES	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-40* is/are pending in the application.

4a) Of the above claim(s) *1-15,21,26,34 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-20,22-25,27-33,35,36 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on February 7, 2008 is acknowledged. Claims 1-16 and 18-40 are currently pending. In the response, Applicant amended claims 16 and 18-20, cancelled claim 17, and added claims 38-40. Claims 1-15, 21, 26, 34, 37, and the non-elected sequences are withdrawn from consideration as being drawn to a non-elected invention.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims. Accordingly, this Office Action is made FINAL.

Election/Restrictions

2. This application contains claims 1-15, 21, 26, 34, 37, and non-elected sequences (SEQ ID NO: 4, 5, & 8) drawn to an invention nonelected with traverse in the reply filed on June 18, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on February 26, 2008 is acknowledged. A signed copy is enclosed.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 40 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 40 is directed to a product of nature, specifically a nucleic acid. Although the oligonucleotide recited in claim 40 contains the nucleotide analog inosine, inosine-containing nucleic acids are found in nature (see page 121 of Dong et al. Mutation Research (2006) 594: 120-134). Amendment of the claims to indicate that the claimed oligonucleotide primers and probes are "isolated and purified" would overcome this rejection.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 16, 22, 23, 25, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Weimer (US 6,248,526 B1; cited previously).

These claims are drawn to a kit comprising at least one primer or probe that specifically anneals to the 5' non-coding region (5' NCR) of the HCV-1 genome.

Regarding claim 16, Weimer teaches a kit for detecting HCV-1 in a sample comprising a primer that specifically anneals to the 5' NCR of the HCV-1 genome (see Example 1 at column 6, lines 1-29, where SEQ ID NO: 1-3 of Weimer anneal to the 5' NCR of HCV-1). Weimer teaches packaging these reagents in a kit at column 5, lines 50-60.

Regarding claim 22, the primer taught by Weimer inherently allows for amplification by PCR or RT-PCR (see Example 1, column 6, lines 1-29).

Regarding claims 23 and 25, Weimer teaches design of primers that target a conserved region of a virus such as HCV (column 5, lines 3-7 teach primer design from conserved regions; column 6, lines 1-29 teach amplification using SEQ ID NO: 1 as a primer, which targets a conserved region of HCV; column 5, lines 50-60 teach kits comprising the disclosed primers and amplification reagents). SEQ ID NO: 1 of Weimer is a universal primer suitable for isolating HCV from all HCV genotypes.

Regarding claim 29, Weimer teaches that the kit further contains reagents sufficient for detection by fluorescence where specific amplification of HCV causes fluorescence of a probe (see Example 1, lines 1-29 and the sequence listing where Weimer teaches that amplification of HCV results in release of the 3' quencher from SEQ ID NO: 1, thereby permitting detection of the FAM moiety at the 5' end of the sequence; see also column 5, lines 11-40 for further description of the fluorescence detection and column 5, lines 50-60, which teaches packaging of the reagents into kits).

7. Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by Yagasaki et al. (JP 06-121700 A; newly cited).

Claim 39 is drawn to an isolated oligonucloetide consisting of SEQ ID NO: 2 or SEQ ID NO: 3.

Yagasaki teaches an isolated oligonucleotide consisting of SEQ ID NO: 2 (see page 2, where the P-(-)71R oligonucleotide is taught). See also paragraph 7 of the attached machine translation of the cited Japanese language document.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 18 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) in view of Tyagi et al. (US 6,037,130; cited previously).

These claims are drawn to an isolated oligonucleotide comprising SEQ ID NO: 7.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (Figure 1). Regarding claims 18 and 35, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. Nucleotides –134 to –118 in this sequence match the 3' region of the claimed SEQ ID NO: 7 (see below).

```
Bukh        -134 CCGCTCAATGCCTGGAG -118
                 ||||||||||||||||
SEQ ID NO: 7     CCGCTCAATGCCTGGAG
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for

design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach an oligonucleotide comprising SEQ ID NO: 7.

Tyagi teaches wavelength-shifting molecular beacon primers (column 2, lines 29-44). Regarding claims 18 and 35, the hairpin region of the molecular beacon primer taught by Tyagi exactly matches the 5' portion of the claimed sequence (see column 18, where SEQ ID NO: 12 of Tyagi contains the sequence 5'-FAM-caccttcaccctcagaagg-DABCYL-g). Tyagi further teaches that the DABCYL quencher may be substituted with methyl red (column 5, lines 32-36). Tyagi teaches that the wavelength-shifting molecular beacon primers produce a greater signal with less background noise than conventional hairpin primers (column 2, lines 1-21).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to synthesize an oligonucleotide comprising SEQ ID NO: 7. An ordinary artisan would have been motivated to design an oligonucleotide from any portion of the 5' noncoding sequence presented in Figure 1, since Bukh expressly suggested using this sequence alignment for primer design (page 4946). An ordinary artisan also would have been motivated by the teachings of Tyagi to construct a wavelength-shifting molecular beacon primer using the hairpin forming sequence taught by Tyagi in order to obtain a primer capable of generating a large fluorescence signal with minimal background for use in multiplex real-time amplification assays. Combination of the hairpin forming region taught by Tyagi and the HCV-specific portion suggested by Bukh would result in the primer of SEQ ID NO: 7. An ordinary artisan would have had a reasonable expectation of success in designing an oligonucleotide of SEQ ID NO: 7 since synthesis and labeling methods were well known in the art.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to design an oligonucleotide from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible oligonucleotides. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. Therefore, an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the prior art of Bukh and Tyagi. Thus, the oligonucleotides of claims 18 and 35 are *prima facie* obvious in view of the combined teachings of Bukh and Tyagi in the absence of secondary considerations.

10. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262;

cited previously) and further in view of Heid et al. (Genome Research (1996) 6(10): 986-994; cited previously).

Claim 20 is drawn to an oligonucleotide probe comprising SEQ ID NO: 6.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claim 20, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. The complement of nucleotides –93 to –69 in this sequence is highly similar to the claimed SEQ ID NO: 6 (see alignment below).

```
Bukh          -69 CGCGACCCAACACTACTCGGCTAG -92
                  ||| ||||||| ||||| ||||||
SEQ ID NO: 6    1 CGCIACCCAACICTACTIGGCTAG  24
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach an isolated oligonucleotide comprising the claimed probe with inosine substitution at the above positions. Bukh also does not teach dual labeling of the probe with FAM and TAMRA.

Watanabe teaches universal primers for amplification of bacterial sequences (see abstract and page 258). Regarding claim 20, Watanabe teaches that introduction of deoxyinosine at positions where nucleotide mismatches occur between the different target sequences (see page 258). Watanabe teaches that inosine substitution neutralizes the effect of these substitutions on the hybridization properties of oligonucleotide probes (page 258).

Watanabe does not teach a probe doubly labeled with FAM and TAMRA.

Heid teaches methods for quantitative real-time PCR detection. The method of Heid comprises inclusion of an oligonucleotide probe labeled at the 5' end with FAM and the 3' end

with TAMRA in a PCR reaction (page 987, column 2 and page 993, column 1). Heid teaches that during PCR amplification, the probe hybridizes to the amplified product (page 987, column 2). When this product is used as a template for further amplification, the quencher (TAMRA) is cleaved from the probe by the exonuclease activity of the polymerase resulting in an increase in fluorescence signal proportional to amplicon production (page 987, column 2). Heid teaches that PCR product accumulation can be accurately and reproducibly measured in real time by quantifying this fluorescence (see abstract, page 987, column 1, and pages 991-992).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to synthesize an oligonucleotide probe comprising SEQ ID NO: 6. An ordinary artisan would have been motivated to synthesize an oligonucleotide probe comprising any stretch of nucleic acids shown in Figure 1 of Bukh for specific detection of HCV nucleic acids. For universal detection of many different HCV nucleic acids, an ordinary artisan would have been motivated to design the probe from any region shown in the alignment of Bukh to contain a high degree of conservation (*e.g.* the region comprising positions –93 to –69). As discussed above, Bukh expressly suggested designing oligonucleotides, such as primers, from the conserved regions of the 5' noncoding sequence (page 4946). An ordinary artisan also would have been motivated to substitute inosine at those nucleotide positions where variability was observed, since Wantanabe taught that inosine substitution neutralized these sequence differences, thereby permitting universal detection of many sequences (page 258). An ordinary artisan would have been motivated to substitute inosine at the claimed positions in SEQ ID NO: 6, since the alignment of Bukh showed sequence variability at these positions (see Figure 1). Finally, an

ordinary artisan would have been motivated to label the probe with FAM and TAMRA to permit its use in quantitative real-time PCR as suggested by Heid.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to design a probe from any stretch of nucleotides in the known HCV-1 5'noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible probes. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. This alignment also expressly suggested the positions that should be substituted with deoxyinosine to permit universal detection. Since oligonucleotide synthesis and labeling methods were well known in the art, an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when designing and synthesizing the finite number of possible probes suggested by the prior art of Bukh, Watanabe, and Heid. Thus, the probe of claim 20 is *prima facie* obvious in view of the combined teachings of Bukh, Watanabe, and Heid in the absence of secondary considerations.

11. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer et al. (US 6,248,526 B1; cited previously) in view of Hong et al. (WO 02/08447 A2; cited previously).

Claim 24 is drawn to the kit of claim 16, further comprising a primer pair of SEQ ID NO: 2 and SEQ ID NO: 3.

Weimer anticipates claims 16, 22, 23, 25, and 29, as discussed above.

Regarding claim 24, Weimer teaches a primer specific to the 5' noncoding region of HCV-1 that comprises the instant SEQ ID NO: 3, as discussed above (see Example 1, column 6, lines 1-29 and SEQ ID NO: 1 of Weimer in the alignment below):

```
SEQ ID NO: 3                    1 CGTCTAGCCATGGCGTTAG 19
                                  ||||||||||||||||||
SEQ ID NO: 1 of Weimer          2 CGTCTAGCCATGGCGTTAG 20.
```

Weimer does not teach a primer pair comprising SEQ ID NO: 2 and SEQ ID NO: 3.

Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23 and below, where SEQ ID NO: 5 of Hong comprises the instant SEQ ID NO: 2):

```
SEQ ID NO: 2                    1 GCAGTACCACAAGGCCTTTCGC 22
                                  ||||||||||||||||||||||
SEQ ID NO: 5 of Hong            8 GCAGTACCACAAGGCCTTTCGC 29.
```

Hong does not teach a primer pair comprising SEQ ID NO: 2 and SEQ ID NO: 3.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to obtain a primer pair comprising an oligonucleotide of SEQ ID NO: 2 and an oligonucleotide of SEQ ID NO: 3. As discussed above, Weimer taught that a primer comprising SEQ ID NO: 3 was useful for amplifying HCV, and Hong taught that a primer comprising SEQ ID NO: 2 was useful for amplifying HCV. Therefore, an ordinary artisan would have been motivated to use these sequences together as a primer pair for specific amplification of HCV. As

noted in MPEP 2144.07, selection of known materials based on their suitability for the intended use is *prima facie* obvious. An ordinary artisan also would have been motivated to additionally include in the kit of Weimer any primers known to be useful for HCV amplification in order to obtain the ability to amplify different regions of the virus. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary artisan would have been motivated to further include this primer in the kit of Weimer in order to obtain the ability to amplify another region of HCV. An ordinary artisan would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the kit of claim 24 is *prima facie* obvious over Weimer in view of Hong.

12. Claims 27, 38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1; cited previously) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262; cited previously) and further in view of Buck et al. (Biotechniques (1999) 27(3): 528-536; cited previously).

Claim 27 is drawn to the kit of claim 16, wherein the kit contains SEQ ID NO: 1. Claim 38 is drawn to the kit of claim 16, wherein the primer or probe anneals specifically between positions -134 and -118 of the 5' NCR of the HCV-1 genome. Claim 40 is drawn to an oligonucleotide comprising SEQ ID NO: 1.

The teachings of Weimer anticipate claims 16, 23, 25, and 29, as discussed above.

Weimer does not teach that the kit includes SEQ ID NO: 1.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (Figure 1). Regarding claims 27, 38, and 40, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. Nucleotides –134 to –118 in this sequence are highly similar to the claimed SEQ ID NO: 1 with the exception of the inosine in the instantly claimed sequence (see below):

```
Bukh          -134 CCGCTCAATGCCTGGAG -118
                   || |||||||||||||
SEQ ID NO: 1   1 CCICTCAATGCCTGGAG  17.
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach primer comprising SEQ ID NO: 1 with an inosine substitution at the third nucleotide.

Watanabe teaches universal primers for amplification of bacterial sequences (see abstract and page 258). Regarding claims 27 and 40, Watanabe teaches that introduction of deoxyinosine at positions where nucleotide mismatches occur between the different target sequences (see page 258). Watanabe teaches that inosine substitution neutralizes the effect of these substitutions on the hybridization properties of oligonucleotide probes (page 258).

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs,

Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to further include a primer comprising SEQ ID NO: 1 in the kit taught by Weimer. An ordinary artisan would have been motivated to further include any HCV-specific primer in the kit of Weimer in order to obtain the ability to amplify different regions of the virus. An ordinary artisan would have been motivated to design a primer from the 5' noncoding sequence presented in Figure 1 since Bukh expressly suggested using the alignment for primer design (page 4946). An ordinary artisan also would have been motivated to substitute inosine at those nucleotide positions where variability was observed, since Wantanabe taught that inosine substitution neutralized these sequence differences, thereby permitting universal detection of many sequences (page 258). An ordinary artisan would have been motivated to substitute inosine at the third nucleotide in SEQ ID NO: 1, since the alignment of Bukh showed sequence variability at this position (see Figure 1). Since Buck clearly demonstrated the equivalence of primer sequences, an

ordinary artisan would have anticipated a reasonable level of success in designing and using any extension primer designed from the sequence taught by Bukh to specifically amplify and detect HCV.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to design a primer from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible primers. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. This alignment also expressly suggested the positions that should be substituted with deoxyinosine to permit universal detection. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the prior art of Bukh and Watanabe. Thus, the kit of claim 27, the kit of claim 38,

and the oligonucleotide of claim 40 are *prima facie* obvious in view of the combined teachings of Weimer, Bukh, Watanabe, and Buck in the absence of secondary considerations.

13. Claims 19 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1; cited previously) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) and further in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262; cited previously) and further in view of Buck et al. (Biotechniques (1999) 27(3): 528-536; cited previously) and further in view of Hong et al. (WO 02/08447 A2; cited previously).

Claim 19 is drawn to a primer pair comprising SEQ ID NO: 1 and SEQ ID NO: 2. Claim 28 is drawn to the kit of claim 27, comprising the primer pair SEQ ID NO: 1 and SEQ ID NO: 2.

Weimer anticipates claims 16, 23, 25, and 29, as discussed above.

The combined teachings of Weimer, Bukh, Watanabe, and Buck result in the kit of claim 27, as discussed above.

Regarding claim 19, the combined teachings of Bukh and Watanabe suggest a primer comprising SEQ ID NO: 1, as discussed in the previous section.

None of the above references (Weimer, Bukh, Watanabe, Buck) teaches inclusion of a primer comprising SEQ ID NO: 2 in the kit or a primer pair comprising SEQ ID NO: 1 and 2.

Regarding claims 19 and 28, Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, where SEQ ID NO: 5 of Hong comprises the instant SEQ ID NO: 2).

Hong does not teach a primer pair comprising SEQ ID NO: 1 and SEQ ID NO: 2.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to obtain a primer pair comprising an oligonucleotide of SEQ ID NO: 1 and an oligonucleotide of SEQ ID NO: 2. As discussed in the previous section, the combined teachings of Bukh and Watanabe suggest a primer comprising SEQ ID NO: 1 for amplification of HCV. Also, as discussed above, Hong taught that a primer comprising SEQ ID NO: 2 was useful for amplifying HCV. Therefore, an ordinary artisan would have been motivated to use oligonucleotides sequences together as a primer pair for specific amplification of HCV. As noted in MPEP 2144.07, selection of known materials based on their suitability for the intended use is *prima facie* obvious. An ordinary artisan also would have been motivated to additionally include in the kit resulting from the combined teachings of Weimer, Bukh, and Watanabe any primers known to be useful for HCV amplification in order to obtain the ability to amplify different regions of the virus. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary artisan would have been motivated to further include this primer in the kit resulting from the combined teachings of Weimer, Bukh, and Watanabe in order to obtain the ability to amplify another region of HCV. An ordinary artisan would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the primer pair of claim 19 and the kit of claim 28 are *prima facie* obvious in view of the combined teachings of Weimer, Bukh, Watanabe, Buck, and Hong.

14. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1; cited previously) in view of Bukh et al. (Proceedings of the National Academy of

Sciences, USA (1992) 89(11): 4942-4946; cited previously) and further in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262; cited previously) and further in view of Heid et al. (Genome Research (1996) 6(10): 986-994; cited previously).

Claim 30 is drawn to the kit of claim 29, wherein the probe comprises SEQ ID NO: 6.

Weimer anticipates claims 16, 23, 25, and 29, as discussed above.

Weimer does not teach inclusion of a probe comprising SEQ ID NO: 6 in the kit.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (Figure 1). Regarding claim 30, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. The complement of nucleotides –93 to –69 in this sequence is highly similar to the claimed SEQ ID NO: 6 (see alignment below).

```
Bukh          -69 CGCGACCCAACACTACTCGGCTAGC -93
                  ||| ||||||| ||||| |||||||
SEQ ID NO: 6    1 CGCIACCCAACICTACTIGGCTAGT  25
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach an isolated oligonucleotide comprising the claimed probe with inosine substitution at the above positions. Bukh also does not teach dual labeling of the probe with FAM and TAMRA.

Watanabe teaches universal primers for amplification of bacterial sequences (see abstract and page 258). Regarding claim 30, Watanabe teaches that introduction of deoxyinosine at positions where nucleotide mismatches occur between the different target sequences (see page 258). Watanabe teaches that inosine substitution neutralizes the effect of these substitutions on the hybridization properties of oligonucleotide probes (page 258).

Watanabe does not teach a probe doubly labeled with FAM and TAMRA.

Heid teaches methods for quantitative real-time PCR detection. The method of Heid comprises inclusion of an oligonucleotide probe labeled at the 5' end with FAM and the 3' end with TAMRA in a PCR reaction (page 987, column 2 and page 993, column 1). Heid teaches that during PCR amplification, the probe hybridizes to the amplified product (page 987, column 2). When this product is used as a template for further amplification, the quencher (TAMRA) is cleaved from the probe by the exonuclease activity of the polymerase resulting in an increase in fluorescence signal proportional to amplicon production (page 987, column 2). Heid teaches that PCR product accumulation can be accurately and reproducibly measured in real time by quantifying this fluorescence (see abstract, page 987, column 1, and pages 991-992).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to synthesize a probe comprising SEQ ID NO: 6 and include this oligonucleotide probe in the kit taught by Weimer. An ordinary artisan would have been motivated to synthesize an oligonucleotide probe comprising any stretch of nucleic acids shown in Figure 1 of Bukh for specific detection of HCV nucleic acids. For universal detection of many different HCV nucleic acids, an ordinary artisan would have been motivated to design the probe from any region shown in the alignment of Bukh to contain a high degree of conservation (*e.g.* the region comprising positions –93 to –69). As discussed above, Bukh expressly suggested designing oligonucleotides, such as primers, from the conserved regions of the 5' noncoding sequence (page 4946). An ordinary artisan also would have been motivated to substitute inosine at those nucleotide positions where variability was observed, since Wantanabe taught that inosine substitution neutralized these sequence differences, thereby permitting universal detection of

many sequences (page 258). An ordinary artisan would have been motivated to substitute inosine at the claimed positions in SEQ ID NO: 6, since the alignment of Bukh showed sequence variability at these positions (see Figure 1). Finally, an ordinary artisan would have been motivated to label the probe with FAM and TAMRA to permit its use in quantitative real-time PCR as suggested by Heid. Since the kits taught by Weimer were designed to provide reagents for amplification and detection of HCV (column 5, lines 50-60 and column 6, lines 1-29), an ordinary artisan would have been especially motivated to include the probe resulting from the combined teachings of Bukh, Watanabe, and Heid in the kit of Weimer to permit accurate, reproducible, and real-time detection of PCR products generated using the kit components.

Lastly, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to design a probe from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible probes. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. This alignment also expressly suggested the positions that should be

substituted with deoxyinosine to permit universal detection. Since oligonucleotide synthesis and labeling methods were well known in the art, an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when designing and synthesizing the finite number of possible probes suggested by the prior art of Bukh, Watanabe, and Heid. Thus, design of a probe comprising SEQ ID NO: 6 for inclusion in the kit taught by Weimer is *prima facie* obvious in view of the combined teachings of Bukh, Watanabe, and Heid in the absence of secondary considerations.

15. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1; cited previously) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) and further in view of Tyagi et al. (US 6,037,130; cited previously) and further in view of Buck et al. (Biotechniques (1999) 27(3): 526-538; cited previously).

Claims 31 and 32 are drawn to the kit of claim 16, further comprising SEQ ID NO: 7, which is a molecular beacon primer.

Weimer anticipates claims 16, 23, 25, and 29, as discussed above.

Weimer does not teach that the kit includes SEQ ID NO: 7.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claims 31 and 32, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. Nucleotides –134 to –118 in this sequence are highly similar to the 3' region of the claimed SEQ ID NO: 7 (see below).

```
Bukh          -134 CCGCTCAATGCCTGGAG -118
                   ||||||||||||||||
SEQ ID NO: 7       CCGCTCAATGCCTGGAG
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach primer comprising SEQ ID NO: 7.

Tyagi teaches wavelength-shifting molecular beacon primers (column 2, lines 29-44). Regarding claims 31 and 32, the hairpin region of the molecular beacon primer taught by Tyagi exactly matches the 5' portion of the claimed sequence (see column 18, where SEQ ID NO: 12 of Tyagi contains the sequence 5'-FAM-caccttcaccctcagaagg-DABCYL-g). Tyagi further teaches that the DABCYL quencher may be substituted with methyl red (column 5, lines 32-36). Tyagi teaches that the wavelength-shifting molecular beacon primers produce a greater signal and less background noise than conventional hairpin primers (column 2, lines 1-21).

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely

high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to further include a primer comprising SEQ ID NO: 7 in the kit taught by Weimer. An ordinary artisan would have been motivated to further include any HCV-specific primer in the kit of Weimer in order to obtain the ability to amplify different regions of the virus. An ordinary artisan would have been motivated to design a primer from the 5' noncoding sequence presented in Figure 1 since Bukh expressly suggested using this alignment for primer design (page 4946). An ordinary artisan also would have been motivated by the teachings of Tyagi to construct a wavelength-shifting molecular beacon primer using the hairpin forming sequence taught by Tyagi in order to obtain a primer capable of generating a large fluorescence signal with minimal background for use in multiplex real-time amplification assays. Combination of the hairpin forming region taught by Tyagi and the HCV-specific portion suggested by Bukh would result in the primer of SEQ ID NO: 7. Since the kits taught by Weimer were designed to provide reagents for amplification and detection of HCV (column 5, lines 50-60 and column 6, lines 1-29), an ordinary artisan would have been especially motivated to include the primer resulting from the combined teachings of Bukh and Tyagi in the kit of Weimer to permit accurate, reproducible, and real-time detection of PCR products generated using the kit components. An ordinary

artisan would have had a reasonable expectation of success in designing and using this primer since synthesis and labeling methods were well known in the art, and also since Buck clearly demonstrated the equivalence of primer sequences.

Finally, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to design a primer from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible primers. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the prior art of Bukh and Tyagi. Thus, the kits of claims 31 and 32 are *prima facie* obvious in view of the combined teachings of Weimer, Bukh, Tyagi, and Buck in the absence of secondary considerations.

16. Claims 19 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1; cited previously) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) and further in view of Tyagi et al. (US 6,037,130; cited previously) and further in view of Buck et al. (Biotechniques (1999) 27(3): 526-538; cited previously) and further in view of Hong et al. (WO 02/08447 A2; cited previously).

Claim 19 is drawn to a primer pair comprising SEQ ID NO: 2 and SEQ ID NO: 7. Claim 33 is drawn to the kit of claim 16 comprising SEQ ID NO: 2 and SEQ ID NO: 7.

Weimer anticipates claims 16, 23, 25, and 29, as discussed above.

The combined teachings of Weimer, Bukh, Tyagi, and Buck result in the kit of claims 31 and 32, as discussed above.

Regarding claim 19, the combined teachings of Bukh and Tyagi suggest a primer comprising SEQ ID NO: 7, as discussed above.

None of the above references (Weimer, Bukh, Tyagi, Buck) teaches inclusion of a primer comprising SEQ ID NO: 2 in the kit or a primer pair comprising SEQ ID NO: 2 and 7.

Regarding claims 19 and 33, Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, where SEQ ID NO: 5 of Hong comprises the instant SEQ ID NO: 2).

Hong does not teach a primer pair comprising SEQ ID NO: 7 and SEQ ID NO: 2.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to obtain a primer pair comprising an oligonucleotide of SEQ ID NO: 7 and an oligonucleotide of SEQ ID NO: 2. As discussed in the previous section, the combined teachings

of Bukh and Tyagi suggested a primer comprising SEQ ID NO: 7 for amplification of HCV. Also, as discussed above, Hong taught that a primer comprising SEQ ID NO: 2 was useful for amplifying HCV. Therefore, an ordinary artisan would have been motivated to use these two oligonucleotide sequences together as a primer pair for specific amplification of HCV. As noted in MPEP 2144.07, selection of known materials based on their suitability for the intended use is *prima facie* obvious. An ordinary artisan also would have been motivated to additionally include in the kit resulting from the combined teachings of Weimer, Bukh, Tyagi, and Buck any primers known to be useful for HCV amplification in order to obtain the ability to amplify different regions of the virus. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary artisan would have been motivated to further include this primer in the kit resulting from the combined teachings of Weimer, Bukh, Tyagi, and Buck in order to obtain the ability to amplify another region of HCV. An ordinary artisan would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the primer pair of claim 19 and the kit of claim 33 are *prima facie* obvious in view of the combined teachings of Weimer, Bukh, Tyagi, Buck, and Hong.

17. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited previously) in view of Tyagi et al. (US 6,037,130; cited previously) and further in view of Hong et al. (WO 02/08447 A2; cited previously).

The combined teachings of Bukh and Tyagi result in the oligonucleotide of claim 35, as discussed above.

Regarding claim 36, Tyagi teaches inclusion of the wavelength-shifting molecular beacon primers in kits (see claims 1, 13, and 22, for example).

Neither Bukh nor Tyagi teaches inclusion of a primer comprising SEQ ID NO: 2 in the kit.

Regarding claim 36, Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, as discussed in greater detail above, where SEQ ID NO: 5 comprises the instant SEQ ID NO: 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to include a primer of SEQ ID NO: 2 in the kit resulting from the combined teachings of Bukh and Tyagi. An ordinary artisan would have been motivated to include in the kit taught by Tyagi any primers known to be useful for amplification in order to obtain the ability to amplify different target nucleic acids. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary artisan would have been motivated to further include this primer in the kit resulting from the combined teachings of Bukh and Tyagi. An ordinary artisan would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the kit of claim 36 is *prima facie* obvious in view of the combined teachings of Bukh, Tyagi, and Hong.

Response to Arguments

18. Applicant's arguments, see page 12, filed on February 7, 2008, with respect to the objections to the specification, have been fully considered and are persuasive. Applicant's amendments have overcome the objections, and therefore, they have been withdrawn.

Applicant's arguments, see page 13, filed on February 7, 2008, with respect to the rejection of claims 18-20, 35, and 36 under 35 U.S.C. 101, have been fully considered and are persuasive. Applicant's amendments have obviated the rejection of claims 18 and 19, and the arguments presented on page 13 were persuasive with respect to claims 20, 35, and 36. Accordingly, the rejection has been withdrawn.

Applicant's arguments regarding the rejection of claims 16, 18, 22, 23, 25, and 29 under 35 U.S.C. 102(b) as being anticipated by Weimer have been fully considered, but they were not persuasive. In view of the amendment, this rejection is currently applicable to claims 16, 22, 23, 25, and 29. Applicant argues that Weimer does not teach all of the elements of claim 16, specifically the requirement that at least one primer or probe in the claimed kit anneal specifically to the 5' non-coding region of the HCV-1 genome (see page 14). This argument was not found persuasive, because as discussed above, SEQ ID NO: 1-3 taught by Weimer anneal specifically to the 5'-noncoding region of the HCV-1 genome. In claim 16, the broadest reasonable interpretation of the term "anneal specifically" includes primers that do not contain mismatches relative to the 5' NCR of HCV-1. Therefore, the term "anneal specifically" does not exclude primers that function as universal primers so long as the universal primers hybridize to the 5' NCR of HCV-1 without mismatches. Since the primers taught by Weimer anneal specifically (*i.e.* without mismatches) to the 5' NCR of HCV-1, they anneal specifically to this

region of the HCV-1 genome, and therefore, claims 16, 22, 23, 25, and 29 remain rejected under 35 U.S.C. 102(b) as being anticipated by Weimer.

Applicant's arguments, see page 15, filed on February 7, 2008, regarding the rejection of claim 18 under 35 U.S.C. 102(b) as being anticipated by Hong, have been fully considered and are persuasive. Hong does not anticipate claim 18 as amended, and therefore, the rejection has been withdrawn.

Applicant's arguments regarding the rejection of claims 19 and 33 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Weimer, Bukh, Tyagi, Buck, and Hong and the rejection of claim 35 under 35 U.S.C. 103(a) as being unpatentable over Bukh in view of Tyagi have been fully considered, but they were not persuasive. Applicant argues that the combined teachings of Bukh and Tyagi do not suggest an oligonucleotide comprising SEQ ID NO: 7 (see pages 22-23). More specifically, Applicant argues that Tyagi teaches away from the claimed oligonucleotide by teaching a 3' target-complementary portion of at least 18 nucleotides, although the claimed oligonucleotide has a 17 nucleotide target-complementary portion (pages 22-23). This argument was not found persuasive, because as noted in MPEP 2141.02 and 2145, a reference only "teaches away" if it actively discredits, discourages, or disparages the proposed solution. In this case, Tyagi does not discourage, discredit, or disparage target-complementary regions shorter than 18 nucleotides, such as the proposed 17 nucleotide target-complementary portion. Rather, Tyagi teaches that this parameter is a results-effective variable that should be optimized by the experimenter to maximize the results of the assay (see column 5, lines 1-20). Since Applicant's arguments were not found persuasive, the rejections under 35 U.S.C. 103(a) have been maintained.

Applicant's arguments regarding the rejection of claim 20 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Bukh, Watanabe, and Heid have been fully considered, but they were not persuasive. Applicant argues that the alignment of Bukh shows an additional mismatch site, and therefore, based on the combined teachings of the cited references, the resulting oligonucleotide would possess inosine substitutions at all variable positions (see page 17). This argument was not persuasive, because the teachings of Watanabe do not suggest that inosine should be substituted at every variable position. Rather, the teachings of Watanabe suggest that inosine substitution should be done at a subset of variable positions (see Table 1 and Figure 1, where the inosine-containing primers I-341f and I-926r do not contain inosine at all of the variable positions). Therefore, an ordinary artisan would have been motivated by the teachings of Watanabe to substitute inosine at a subset of the mismatched positions identified by the alignment of Bukh (*e.g.* the three positions in SEQ ID NO: 6) with a reasonable expectation of success. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Applicant's arguments regarding the following rejections have been fully considered, but they were not persuasive: (1) the rejection of claims 19 and 24 under 35 U.S.C. 103(a) as being unpatentable over Weimer in view of Hong, (2) the rejection of claim 30 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Weimer, Bukh, Watanabe, and Heid, (3) the rejection of claims 31 and 32 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Weimer, Bukh, Tyagi, and Buck, and (4) the rejection of claim 33 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Weimer, Bukh, Tyagi, Buck, and Hong. Applicant argues that Weimer does not teach all of the elements of claim 16,

from which the above claims depend, and that the cited secondary references do not overcome this deficiency in the primary reference (see pages 15, 16, and 20-23). This argument was not found persuasive, because as discussed above, Weimer teaches all of the elements of claim 16. Since Applicant's arguments were not found persuasive, the rejections have been maintained.

Applicant's arguments regarding the rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Weimer, Bukh, Wantanabe, and Buck and the rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Weimer, Bukh, Watanabe, Buck, and Hong have been fully considered, but they were not persuasive. Applicant argues that Bukh teaches away from designing primers from the region of the 5' non-coding region comprising SEQ ID NO: 1 (see page 18). Applicant also argues that the combined teachings of the cited references do not suggest which variable positions should be chosen for inosine substitution (pages 18-20). Applicant's arguments were not found persuasive, because the rejection is based on the combined teachings of the references. Based on the combined teachings of the references, an ordinary artisan would have been motivated to design a primer from the variable region of the 5' NCR identified by Bukh and would have substituted inosine at the claimed position with a reasonable expectation of success. Since Watanabe taught that inosine substitution could be used to overcome the effect of variable nucleotides, an ordinary artisan would have been motivated to design primers from the claimed region of the HCV-1 5' NCR with a reasonable expectation of success. Also, since Watanabe does not teach that all variable positions must be substituted with inosine (see Figure 1 and Table 1, where the I-341f and I-926r primers do not contain inosine at every variable position), an ordinary artisan would have been motivated to substitute inosine at a subset of the mismatched positions identified by

the alignment of Bukh (*e.g.* the single substation in SEQ ID NO: 1) with a reasonable expectation of success. Since Applicant's arguments were not found persuasive, the rejections have been maintained.

Applicant's arguments regarding the rejection of claim 36 under 35 U.S.C. 103(a) as being unpatentable over Bukh in view of Tyagi and further in view of Hong have been fully considered, but they were not persuasive. Applicant argues that the combined teachings of Bukh and Tyagi do not teach or suggest the oligonucleotide of claim 35, and that Hong does not overcome this deficiency in the primary reference (pages 23-24). This argument was not found persuasive, because as discussed above, the combined teachings of Bukh and Tyagi suggest the oligonucleotide of claim 35. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Conclusion

19. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

amb
/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637